REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-10 are in this case. Claims 1,2 and 7-10 have been withdrawn from consideration. Claims 3-6 have been rejected. No Claims have been allowed. Claims 4-6 have been cancelled. Claim 3 has now been amended.

Information Disclosure Statement

In accordance with the requirements of 37 CFR 1.9(b), an Information Disclosure Statement, as required by the Examiner, is being submitted under a separate cover.

35 U.S.C. §112, First Paragraph, Rejections

The Examiner has rejected claims 3-6 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to make and/or use the invention. The Examiners rejections are respectfully traversed. Claims 4-6 have now been cancelled, rendering moot the Examiner's rejection thereof. Claim 3 has now been amended.

The Examiner has stated that while the specification clearly discloses no detectable expression of the hpa gene in peripheral white blood cells from CML and NHL patients, and positive expression in cells from all of the AML and ALL patients, one of ordinary skill would be unable to distinguish whether a patient had AML or ALL solely based on expression of hpa in peripheral white blood cells. The Examiner further states that additional factors, such as the methods of Diagnosing AML, ALL, CML and NHL taught in the Merck Manual, would be necessary for determining whether a patient has one of said diseases.

The present invention is of heparanase specific molecular probes which can be used detection and monitoring of malignancies, metastases, and non-malignant conditions, specifically as a novel method of distinguishing between different types of hematopoietic tumors. While reducing the present invention to practice, the inventors measured the expression of heparanase in purified peripheral white blood cells of patients with a variety of blood cell disorders, and unexpectedly uncovered that cells from all patients having ALL and AML expressed the gene, while no

1/3 tested positive

expression was detected in the cells from any of the CML or NHL patients (see Table 1, page 57, line 23 to page 58, line 10, and Figures 13, 14 and 15). These surprising results, indicating absolute mutual exclusion of heparanase expression between the two groups of disease, now provide a previously unavailable means with which to make a clinically accurate distinction between differentiated B cell lymphoma such as CLL and NHL, and undifferentiated myelocytic and lymphoblastoid leukemia such as ALL and AML. Indeed, as noted by the Examiner, the art at the time the invention was made does not show any method comprising expression of a heparanase gene to determine if a patient has CLL, CML, ALL or NHL, acknowledging the novel and important contribution of the present invention to detection and treatment of blood cancers.

There is a strongly felt need for improved methods of blood cell cancer diagnostics, in the early stages of detection. Clinical signs of leukemia or lymphoma include generalized symptoms such as weight loss, fatigue, fever, loss of appetite, which are often misdiagnosed, or, as in the case of chronic lymphocytic leukemia (CLL), may even be so mild as to often be undetected. Once a blood cell count and examination is performed, the predominance of abnormal white blood cells can be recognized. However, distinction between different groups of blood cell cancer cannot be positively determined by such examination, and invasive bone marrow aspiration and biopsy is presently required for further diagnosis.

By measuring the expression of the hpa gene in easily attainable peripheral white blood cells of patients having clinical symptoms of a blood cancer condition (such symptoms as described, for example, in the relevant sections of the Merck Manual), the methods of the present invention can clearly distinguish between CLL and NHL, on the one hand, and ALL and AML on the other, before resorting to more costly and invasive methods. Thus, a timely diagnosis can ameliorate patient anxiety and help reduce morbidity and mortality.

To further clarify and define the scope of the present invention, and to expedite prompt prosecution in this case, Applicant has chosen to amend claim 3 to include the limitations: "A method of diagnosing CLL or NHL..." and "...in a human individual suspected of having a blood cancer...", thus restricting the invention to diagnosis following, or concomitant with, other, commonly recognized signs of blood cell cancers. Further, now amended claim 3 restricts the invention to

diagnosing CLL or NHL, rather than providing diagnosis of the individual diseases in each group.

The Examiner further states that the expression of hpa in blood cells other than white blood cells has not been tested, that expression of heparanase other than human heparanase has not been tested, and that no heparanase other than that encoded by instant SEQ ID NO:1 has been disclosed tested in the present specification. Thus, Examiner concludes that it would require undue experimentation for one of skill in the art to use the recited methods comprising "any heparanase..., any blood cells..., in any species other than human, without consideration of other diagnostic indicators" to determine if a patient has CLL, AML, ALL or NHL. The Examiner's rejection is respectfully traversed.

Applicant wishes to point out that the detection of expression of human heparanase in peripheral white blood cells correlates exactly with the presence or absence of any heparanase activity present in these cells (see page 56, lines 5-9), indicating that heparanase catalytic activity is the result of expression of the genes comprising sequences of instant SEQ ID NO: 1. No heparanase gene expression, nor heparanase activity is detected in CLL cells, while AML and CML cells readily express and secrete the enzyme; in other words, the distinction between the two groups of cells is qualitative rather than quantitative. Thus, one of ordinary skill in the art, in possession of the teachings of the present invention, would readily be capable of determining a differentiating level of expression of heparanase in CLL and NHL as opposed to AML and ALL, using the recited methods comprising any heparanase (other than human heparanase) including heparanase other than that encoded by SEQ ID NO: 1, without resorting to undue experimentation.

The abovementioned notwithstanding, to further clarify and define the scope of the present invention, and to expedite prompt prosecution in this case, in addition to the abovementioned amendments, Applicant has chosen to amend claim 3 to include the limitations: "diagnosing CLL or NHL in a human individual...", "...the method comprising monitoring an expression of heparanase in white blood cells of the individual..." (emphasis added), thus limiting the method of the present invention to detection of expression of the human heparanase gene, and detection in white blood cells.

In view of the above arguments and amendments, Applicant believes to have overcome the 35 U.S.C. § 112, first paragraph rejections.

35 U.S.C. § 112, Second Paragraph Rejections

The Examiner has rejected claims 3-6 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claims 4-6 have now been canceled, rendering moot the Examiner's rejection thereof. Claim 3 has now been amended.

With respect to claims 3-6 the Examiner points out that the recitation of the phrase "a patient" in line 3 of each claim is unclear.

Claim 3 has now been amended to recite: "a human individual..." in the preamble, and "...the individual..." thereafter in the claim, as recommended by the Examiner, thus overcoming the 35 USC 112, second paragraph rejection.

In view of the above amendments and remarks it is respectfully submitted that claim 3 is now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

An early and favorable action is therefore respectfully requested.

Respectfully submitted,

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